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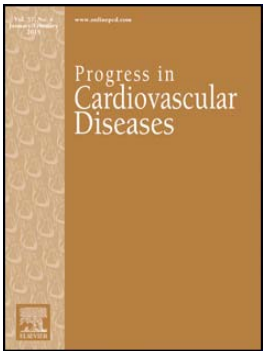
DOI:
10.1016/j.pcad.2015.09.005

Document Version
Peer reviewed version

Citation for published version (Harvard):
Shantsila, E & Lip, GYH 2016, 'Preventing Thrombosis to Improve Outcomes in Heart Failure Patients', *Progress in Cardiovascular Diseases*, vol. 58, no. 4, pp. 386-392. https://doi.org/10.1016/j.pcad.2015.09.005



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PII: S0033-0620(15)30018-9
DOI: doi: 10.1016/j.pcad.2015.09.005
Reference: YPCAD 690

To appear in: *Progress in Cardiovascular Diseases*

Please cite this article as: Shantsila Eduard, Lip Gregory Y.H., Preventing Thrombosis to Improve Outcomes in Heart Failure Patients, *Progress in Cardiovascular Diseases* (2015), doi: 10.1016/j.pcad.2015.09.005

Review

Preventing Thrombosis to Improve Outcomes in Heart Failure Patients

Running title: Thrombosis in Heart Failure

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Disclosure/COI:None

Abstract

Heart failure (HF) is associated with an increased risk of thrombotic events, particularly if this condition is accompanied by atrial fibrillation (AF). Many HF patients have background coronary artery disease (CAD) making them prone to coronary thrombosis resulting in myocardial infarction or sudden death. Oral anticoagulation is essential in the vast majority of HF patients with AF with non-vitamin K based anticoagulants being a suitable alternative to warfarin. In contrast, aspirin alone does not provide adequate stroke prevention in such patients. In HF without AF, oral anticoagulation should not be routinely used, and antiplatelet agents should be prescribed in patients with background CAD. This review provides an overview of prothrombotic factors and antithrombotic management of patients with HF.

Key words: heart failure, thrombosis, oral anticoagulants, atrial fibrillation

Abbreviations:

AF: Atrial fibrillation

CAD: Coronary artery disease

HF:Heart failure

HFrEF: Heart failure with reduced ejection fraction

LA: Left atrium or atrial

LAA:Left atrial appendage

LV:Left ventricle or ventricular

LVEF: Left ventricular ejection fraction

NSR:Normal sinus rhythm

NYHA:New York Heart Association

NVAF: Non-valvular atrial fibrillation

SCD:Sudden cardiac death

VTE: Venous thromboembolism

Introduction

Heart failure (HF) has been associated with increased risk of thrombotic events that affected a third of HF patients.[1] Poor mobility and multiple co-morbidities predispose to occurrence of venous thromboembolism (VTE).[2, 3] The risks are particularly high in patients with acute HF decompensation who require hospital admission with VTE reported in up to half of such patients, unless VTE prophylaxis is given.[2, 3] Many HF patients have background coronary artery disease (CAD) making them prone to coronary thrombosis resulting in myocardial infarction or sudden cardiac death (SCD).[4] Patients with HF are also at increased risk of ischaemic stroke, which has been reported to occur in 2% of such patients within the first year of presentation.[5] In fact, about 20% of patients with ischemic stroke have impaired left ventricular (LV) systolic function.[6]

The risk of stroke and systemic VTE is especially high in patients with concomitant atrial fibrillation (AF), which is extremely common in subjects with HF irrespectively of LV ejection fraction (LVEF). Literature suggests that up to 40% of HF patients may experience the arrhythmia.[7, 8] In patients with HF and preserved LVEF , AF was associated with approximately 3-fold higher risk of ischaemic stroke compared to those with no history of the arrhythmia.[9] In patients with HF with reduced LVEF (HFrEF),the presence of AF carries a 2-fold increased risk of ischaemic stroke and systemic VTE compared to those in normal sinus rhythm (NSR).[10] All major clinical guidelines on management of AF recognise HF as a major risk factor for stroke.[11, 12]

Moreover, the true rate of AF can be underestimated due to possibility of 'silent' AF. A retrospective analysis of multicentre trials of cardiac resynchronization therapy in HF demonstrated the presence of AF episodes in a third of patients and it was frequently 'silent'.[13] The study also showed that even short (e.g., 10 min) paroxysms of 'silent' AF might have significant clinical consequences, being associated with 2-fold increased risk of deaths or hospital admission for HF.

The prothrombotic state in heart failure

Congestive HF and AF share a number of common pathophysiological processes producing a multifactorial prothrombotic milieu.

First, both HF and AF are characterized by impaired cardiac and/or systemic haemodynamics predisposing to blood stasis. In AF atrial stasis is caused by lack of synchronous contractility of atrial cardiomyocytes, resulting in absence of efficient atrial systole. The stasis is most prominent within the left atrial (LA) appendage (LAA), which has no 'through flow' and where the blood flow ultimately depends on efficient synchronous contraction of the appendage cardiomyocytes. It is not surprising that the LAA is the most frequent site of thrombus formation in AF;[14] LA dilation has been shown to be independently associated with increased risk for stroke even after adjustment for other recognized stroke risk factors.[15, 16] The right atrial appendage is less prone to thrombus generation as it is smaller and shallower than its left sided counterpart. Intracardiac blood stasis in AF is reflected by increased levels of brain natriuretic peptides despite preserved LVcontractility.[17]

Blood stasis in AF is not solely restricted to the atria and AF does contribute to systemic stasis as absence of atrial systole disturbs LV diastolic filling and cardiac stroke volume. The impact is even more prominent when it occurs in the presence of other conditions predisposing to local or systemic blood stasis.

Flow congestion in HF is clearly noticeable within the failing LV especially if patients have severe regional wall motion abnormalities in the apical area (e.g., in post myocardial infarction aneurism). Severe deterioration in systolic LV function leads to peripheral congestion and severe blood stasis.

In fact, HF frequently co-exists with AF, with 13 to 40 per cent of HF patients having AF irrespectively of LVEF.[7, 8] Atrial fibrillation potentiates intracardiac and extracardiac blood stasis in patients with HF, thus predisposing to stroke and systemic VTE. Occurrence of AF in HF further deteriorates already impaired systemic perfusion as effective atrial contraction in sinus rhythm contributes up to 25% of the cardiac output.[18 19]

Second, patients with HF have prominent endothelial dysfunction, irrespectively of HF aetiology.[20] The presence of endothelial dysfunction in HF bears increased mortality and risk of hospital re-admissions. Endothelial dysfunction parallels and predisposes to chronic proinflammatory state and increased oxidative stress, which promotes thrombogenesis.[21, 22] Presence of congestive HF further augments endothelial dysfunction already evident in HF.[21-23] Small areas of endothelial

denudation and thrombus formation have been described in atrial fibrillation complicated by cerebral embolism.

Third, the final component of Virchow's triad in HF is evident by an imbalance in pro- and antithrombotic factors with clear prothrombotic shift overall. Patients with HF have increased levels of plasma fibrinogen, fibrinopeptide A and fibrin D-dimer.[21, 24, 25] Furthermore, the presence of endothelial dysfunction in HF has profound implication on production of haemostatic and fibrinolytic factors in HF with net effect favouring prothrombotic changes[20, 26]

Thrombosis prevention in heart failure with atrial fibrillation

In almost 100,000 patients admitted with HF and enrolled in Get With The Guidelines-HF programme, AF was independently associated with poor outcome.[27] Current guidelines on management of patients with AF suggest administration of oral anticoagulation in virtually all HF patients without contraindications.[28, 29] Indeed, HF per se puts patents in the category of CHA_2DS_2-VASc score ≥ 1, where oral anticoagulation is advisable with majority of patients having at least one other risk factor thus making oral anticoagulation mandated (i.e., score ≥ 2). As a result oral anticoagulation should be routinely used in HF with concomitant AF.[28, 30]

All patients started on oral anticoagulation with warfarin or other vitamin K antagonists must have regular monitoring of international normalised ratio (INR), with target recommended INR value of 2.0-3.0 in non-valvular AF (NVAF).[31, 32]

Anticoagulation with warfarin brings many challenges, given the high inter- and intra-patient variability in INRs, requiring regular anticoagulation monitoring. A high time in therapeutic range (TTR, ie. >70%) is needed to ensure the best outcomes in efficacy and safety[33-35]; TTRs can be influenced by multiple clinical risk factors, which have been incorporated into the SAMe-TT_2R_2 score to help identify those patients who are likely to do well on warfarin[36-38].

Real world data indicate that oral anticoagulation in AF is often underutilised, with fear of perceived risk of bleeding complications being the most common reason of not prescribing of the indicated treatment.[26] Although oral anticoagulants should be avoided in patients with genuine high risk of bleeding (e.g., coagulopathy) such patients are uncommon. To avoid inadequate stroke prevention in HF accompanied by AF, all such patients should have bleeding risk quantification using the recommended HAS-BLED score.[28, 39, 40] In subjects with HAS-BLED score ≥3, risks and benefits of oral anticoagulation should be individually considered and if started the therapy needs to be regularly reviewed to ensure its safety.

Although aspirin is frequently used in patients with HF and NSR, it does not provide adequate protection against stroke or systemic VTE in people with AF. In those few patients where oral anticoagulants are genuinely contraindicated due to high risk of bleeding, aspirin bears similar risk of bleeding to warfarin without providing effective prevention of VTE events; and it should be avoided unless the patient has CAD.

In view of the profound difference in the risk of stroke and systemic VTE between HF patients with and without AF, should restoration of NSR be the goal in patients with persistent AF? A comparison of the two approaches was performed in the randomised Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study [41]. The trial recruited 1376 patients with LVEF <35% who were followed for an average of 3 years. The study found no difference in rates of stroke between the two groups (p=0.68), although the event rates were low (1% in the rhythm-control group and 2% in the rate control group).

Several other trials did not find any significant benefit of rhythm control vs. rate control strategy for stroke prevention in AF. Although these studies were not specifically designed for patients with HF, such subjects represented a substantial fraction of their participants. The How to Treat Chronic Atrial Fibrillation (HOT CAFE) study [42] involved patients with mild-moderate HF, but about half of the participants had mild HF with New York Heart Classification (NYHA) class I. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, only 26% of participants had impaired LVEF and 23% of subjects had history of congestive HF (only 9% of all patients had NYHA functional class ≥II, average LVEF was 55%).[43] In the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation RACE [44] trial with about a half of the 512 participants having a history of symptomatic HF, there was no evidence of superiority of any of the two approaches and adequate rate control may be appropriate for patients with HF.

Thrombosis prevention in heart failure without atrial fibrillation

The pattern of thrombotic complications in HF differs substantially between subjects with and without AF. Whilst cardiogenic stroke and systemic thromboembolism is the major risk in patients with AF, in those without AF risks related to coronary thrombosis dominate. In HF subjects without any history of AF who had NYHA class II-III symptoms, the annual rate of systemic VTE was about 1%, which would correspond to low risk in patients with AF.[45] However the risks may be much higher in selected HF groups, such as those with advanced congested HF with poor mobility.[7, 8] In subanalysis of the Survival and Ventricular Enlargement (SAVE) trial, risk of ischaemic strokes increased by 18% for every 5% reduction in LVEF.[46] In fact, impact of deterioration of left ventricular contractility on VTE risk may be more prominent in HF in NSR than in those with AF; and in the Sudden Cardiac Death-HF (SCD-Heft) study, this association was noted in subjects in NSR only.[47] Patients with severe HF could be more prone to eventually develop AF, which might not be timely reported to clinicians.

Several trials have aimed to establish utility of oral anticoagulants in HF with NSR.[15-17] In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study, patients with impaired left ventricular systolic function (i.e., left ventricular ejection fraction <30%) were randomised for warfarin or antiplatelet therapy.[16] The trial showed a trend towards lower annual rates of non-fatal stroke in the warfarin group (0.7%) compared to aspirin (2.1%) group and lower and similar trend for hospital admission (16.1% in the warfarin group vs. 22.2 % in aspirin group and 18.3% in clopidogrel group). The positive trend was offset by a significant increase in bleeding complications (5.5 % with warfarin vs. 3.6% with aspirin and 2.5% with

clopidogrel). Unfortunately, the study lacked statistical power needed to make unambiguous conclusions.

The Warfarin Aspirin Reduced Cardiac Ejection Fraction (WARCEF) study was the largest trial of oral anticoagulation in HF with NSR. It recruited 2305 patients with HFrEF. During mean follow up of 3.5 years, treatment with warfarin as compared to 325 mg daily dose of aspirin had no impact on the primary outcome of ischemic stroke, intracerebral haemorrhage, or any-cause death.[48] In accordance with the WATCH trial, treatment with warfarin in the WARCEF study was associated with reduction in ischemic strokes (hazard ratio 0.52; 95% confidence interval 0.33-0.82; p=0.005) by the price of almost doubled rate of major bleedings (no difference in intracranial or intracerebral was noted). In view of lack of any convincing overall benefit of warfarin in patients in NSR, current consensus does not recommend oral anticoagulant therapy with vitamin K antagonists in AF-free HF.[1]

As mentioned above, patients with HF in NSR often have background CAD and are at high risk of coronary atherothrombotic events. They should receive appropriate antiplatelet therapy (typically aspirin with addition of an ADP-inhibitor after percutaneous coronary interventions and/or acute coronary syndrome). Of note, about half of cases of SCD in HF are related to coronary atherothrombosis, and over a quarter of admissions with acute HF have features of coronary thrombosis, thus mandating strict compliance with the recommended antiplatelet regimens.[10] Favourable safety and efficacy profile of non-vitamin K oral anticoagulants may overcome limitations of warfarin in AF-free HF, but this needs to be assessed in appropriately designed clinical trial(s).

Non-vitamin K oral anticoagulants for use in atrial fibrillation with heart failure

Non-vitamin K oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants[49]) directed to block activity of specific coagulation factors responsible for activation of both intrinsic and extrinsic coagulation pathways have been recently approved for stroke prevention in NVAF (Table 1).

Whilst showing efficacy, safety and relative convenience compared to warfarin, the NOACs have their own challenges, especially in translating the impressive clinical data to everyday clinical practice[50-52].

Apixaban

Apixaban is a selective reversible inhibitor of factor Xa. Its effectiveness and safety in AF was established in a large Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) double-blind noninferiority randomised study comparing apixaban (5 mg twice-daily standard dose) with warfarin adjusted to maintain INR 2.0-3.0.[53] (Table 2) All trial patients had at least one additional risk factor for stroke. Among 18,201 study participants 35% had HF defined as symptomatic HF or LVEF <40%. This study showed that the risk of stroke and systemic VTE was equal in the two treatment arms, irrespectively of presence of HF (Table 3). The presence of HF also did not affect risk of major bleeding, which was similar with both treatments. Bleeding complications annually occurred in 2.2% of

HF-free patients receiving apixaban, 1.9% of subjects with HF treated with apixaban and 3.1% of patients treated with warfarin (with or without HF).

The ARISTOTLE trial has demonstrated increased risk of the combined end point of stroke, systemic VTE or death in patients with HF who have LVEF < 40% (8.1 per 100 patient-years) compared to 5.32 per 100 patient-years in symptomatic HF with LVEF > 40%, and 1.54 per 100 patient-years in participants with no HF and normal LVEF($p<0.0001$ for all comparisons). Despite this apixaban effectiveness was consistent among the three groups.[54]

Rivaroxaban

Rivaroxaban is a factor Xa inhibitor with concentration-dependent anticoagulation effect on oral intake.[55, 56] The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial provided double-blinded randomised comparison of rivaroxaban 20 mg once daily (15 mg daily creatinine clearance was 30-49 ml/min) or warfarin adjusted to maintain INR 2.0-3.0 in 14264 patients with AF.[55]; the study included 62.5% of patients with HF. Subjects with HF, as compared to those without HF, more frequently had persistent AF (83% and 78%, respectively) and had higher average $CHADS^2$ score (3.7 and 3.1, respectively). Rivaroxaban showed similar effectiveness in people with LVEF < 40% and in those with higher LVEF. The agent maintained equal efficacy and safety profiles among patients with NYHA class III-IV symptoms as in those with more mild HF symptoms. Of importance, the favourable properties of rivaroxaban were consistent in HF patients with different risk of stroke or systemic VTE.[57] Moreover, when intention to

treat analysis was applied to patients with HF, rivaroxaban was not associated with any increase in major or non-major clinically relevant bleeding. On the other hand, treatment with rivaroxaban resulted in lower rates of haemorrhagic stroke in HF patients (adjusted hazard ratio 0.38, 95% confidence interval 0.19-0.76).

These findings have been complemented by a study designed to establish pharmacokinetic and pharmacodynamic properties of rivaroxaban in patients admitted with acute decompensated HF, which demonstrated that pharmacological characteristics of the agent in acute HF were not significantly affected by additional thromboprophylaxis with enoxaparin 40 mg daily, which is frequently the current routine practice.[58]

Dabigatran etexilate

Dabigatran is the only oral direct thrombin inhibitor currently used for stroke prevention in AF. The Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) study randomised 18,113 patients with AF, including 4904 patients with symptomatic HF to 110 mg or 150 mg twice daily or open label warfarin (target INR 2.0-3.0).[55]. Patients with HF were younger than HF- free subjects (68±10 vs. 73±8 years, respectively) and included a higher proportion of male participants (66.9% vs. 62.3%).[59] Patients with LVEF ≤40% represented 43.5% of the study cohort and were on average 5 years younger than participants with better LV contractility. There was no significant difference in the rate of stroke of systemic VTE among patients with HF assigned for different treatment regimens (1.90% with 110 mg dabigatran, 1.44 with 150mg dabigatran, and 1.85% with warfarin). The annual rates of major bleedings in patients with HF were 3.26% with 110 mg dabigatran, 3.10% with 150

mg dabigatran and 3.90% with warfarin, confirming a favourable safety profile of dabigatran in HF. However, it was noted that patients with HF tended to have lower median TTR than subjects without HF. The rates of the most feared complication of oral anticoagulation, intracranial bleeding, were lower with the two dabigatran doses (hazard ratio 0.39, 95% confidence interval 0.17-0.89 for dabigatran 150 mg vs. warfarin; hazard ratio 0.34, 95% confidence interval 0.14-0.80 for dabigatran 110 mg vs. warfarin).[59]

Conclusions

Oral anticoagulation is essential in the vast majority of HF patients with AF with non-vitamin K based anticoagulants being suitable alternative to warfarin. In contrast, aspirin alone does not provide adequate stroke prevention in such patients. In HF without AF, oral anticoagulation should not be routinely used, and antiplatelet agents should be prescribed in patients with background CAD. More data on utility of NOACs in HF are awaited with interest.

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Table 1. Pharmacological characteristics of non-vitamin K oral anticoagulants

	Apixaban	Rivaroxaban	Dabigatran
Mode of action	Factor Xa inhibitor	Factor Xa inhibitor	Factor II (thrombin) inhibitor
Dosing	Twice daily	Once daily	Twice daily
Prodrug	No	No	Yes
Bioavailability	60%	More 60-80%	6%
Time to peak level, hours	3	3	2
Half-life, hours	9-14	4-9 (12 in elderly)	14-17
Renal excretion	20-30% (75% faecal)	35% (35% by liver)	80%
Interactions	Potent inhibitors/inducers of CYP3A4 and P-gp	Potent inhibitors/inducers of CYP3A4 and P-gp	Potent inhibitors/inducers of P-gp

Table 2. Characteristics of major trials on non-vitamin K oral anticoagulants in atrial fibrillation

Trial	ARISTOTLE[55]	ROCKET-AF[60]	RE-LY[53]
Active medication	Apixaban	Rivaroxaban	Dabigatran
Participant number	18201	14264	18113
Patients with heart failure (% of total)	2736 (19%)	9033 (64%)	4904 (27%)
Follow-up duration,	2.1	3.5	2.1

years			
Males	2153 (79%)*	5500 (61%)*	3282 (67%)*
Age, years	68 (60-74)	72 (65-78)	68±3
CHADS2 score	2.7±1.1	3.7±0.9	2.6±1.1
Definition of heart failure	Ejection fraction <40% or moderate-severe left ventricular dysfunction	History of heart failure or ejection fraction <40%	NYHA class ≥ II symptoms 6 months prior to screening and previous HF admission
Ischemic etiology of heart failure	763 (28%)*	2685 (30%)*	1559 (32%)*
History of diabetes	736 (27%)*	3828 (42%)*	1298 (27%)*
History of hypertension	2059 (75%)*	8402 (93%)*	3686 (75%)*
Ejection fraction ≤ 40%	Not provided, but 55% had moderate systolic dysfunction; 31% severe systolic dysfunction	2145 (34%)*	44%*
Interraction with HF	No (p=0.50)	No	No (p=0.42/p=0.33 with the 2 doses)

*Per cent of patients with heart failure

Table 3. Outcomes of major trials on non-vitamin K oral anticoagulants in atrial fibrillation

Outcome events, per year	ARISTOTLE		ROCKET-AF		RE-LY	
Agent	Apixaban	Warfarin	Rivaroxaban	Warfarin	Dabigatran	Warfarin
Stroke or systemic thromboembolism	0.99%	1.8%	1.9%	2.1%	1.4%	1.9%
Death	7.0%	7.2%	5.1%	5.5%	Not provided	Not provided
Major bleeding	2.8%	3.4%	Not provided	Not provided	3.1%	3.4%
Intracranial bleeding	0.18%	0.73%	0.4%	0.7%	0.26%	0.65%